This document is scheduled to be published in the Federal Register on 01/21/2022 and available online at **federalregister.gov/d/2022-01147**, and on **govinfo.gov**

4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 886

[Docket No. FDA-2021-N-0993]

Medical Devices; Ophthalmic Devices; Classification of the Retinal Diagnostic Software Device

AGENCY: Food and Drug Administration, Department of Health and Human Services (HHS).

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is classifying the retinal diagnostic software device into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for the retinal diagnostic software device's classification. We are taking this action because we have determined that classifying the device into class II (special controls) will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on April 11, 2018.

FOR FURTHER INFORMATION CONTACT: Elvin Ng, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1304, Silver Spring, MD 20993-0002, 240-402-4662, Elvin.Ng@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the retinal diagnostic software device as class II (special controls), which we have determined will provide a reasonable assurance of safety and effectiveness. In addition, we believe this action will enhance patients' access to beneficial

innovation, by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified as, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (see 21 U.S.C. 360c(f)(1)). We refer to these devices as "postamendments devices" because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act (see 21 U.S.C. 360c(i)) to a predicate device that does not require premarket approval. We determine whether a new device is substantially equivalent to a predicate device by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

FDA may also classify a device through "De Novo" classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act. Section 207 of the Food and Drug Administration Modernization Act of 1997 established the first procedure for De Novo classification (Pub. L. 105-115). Section 607 of the Food and Drug Administration Safety and Innovation Act modified the De Novo application process by adding a second procedure (Pub. L. 112-144). A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a 510(k) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA shall classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

We believe this De Novo classification will enhance patients' access to beneficial innovation. When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i)) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD & C Act, defining "substantial equivalence"). Instead, sponsors can use the less-burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On January 12, 2018, FDA received IDx, LLC's request for De Novo classification of the IDx-DR. FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act.

We classify devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use (see 21 U.S.C. 360c(a)(1)(B)). After review of the information submitted in the request, we determined that the device can be classified into class II with the establishment of special controls. FDA has

determined that these special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on April 11, 2018, FDA issued an order to the requester classifying the device into class II. In this final order, FDA is codifying the classification of the device by adding 21 CFR 886.1100.[1] We have named the generic type of device retinal diagnostic software device, and it is identified as a prescription software device that incorporates an adaptive algorithm to evaluate ophthalmic images for diagnostic screening to identify retinal diseases or conditions.

FDA has identified the following risks to health associated specifically with this type of device and the measures required to mitigate these risks in table 1.

Table 1.--Retinal Diagnostic Software Device Risks and Mitigation Measures

Identified Risks	Mitigation Measures
False positive results leading to additional unnecessary medical procedures • Diagnostic software failure • Software failure	Clinical performance testing; Software verification, validation, and hazard analysis; and Protocol for technical specification changes
False negative results leading to delay of further evaluation or treatment • Diagnostic software failure • Software failure	Clinical performance testing; Software verification, validation, and hazard analysis; Protocol for technical specification changes; and Labeling
Operator failure to provide images that meet input quality specifications	Labeling, Training, and Human factors validation testing

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness. For a device to fall within this classification, and thus avoid automatic classification in class III, it would have to comply with the special controls named in this final order. The necessary special controls appear in the regulation codified by this order. This device is subject to premarket notification requirements under section 510(k) of the FD&C Act.

[1] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

At the time of classification, retinal diagnostic software devices are for prescription use only. Prescription devices are exempt from the requirement for adequate directions for use for the layperson under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) and 21 CFR 801.5, as long as the conditions of 21 CFR 801.109 are met.

III. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations and guidance. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in the guidance document "De Novo Classification Process (Evaluation of Automatic Class III Designation)" have been approved under OMB control number 0910-0844; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval, have been approved under OMB control number 0910-0231; the collections of information in part 807, subpart E, regarding premarket notification submissions, have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820, regarding quality system regulation, have been approved under OMB control number 0910-0073; and the collections of information in 21 CFR part 801, regarding labeling, have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 886

Medical devices, Ophthalmic goods and services.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 886 is amended as follows:

PART 886--OPHTHALMIC DEVICES

1. The authority citation for part 886 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360*l,* 371.

2. Add § 886.1100 to subpart B to read as follows:

§ 886.1100 Retinal diagnostic software device.

(a) *Identification*. A retinal diagnostic software device is a prescription software device that incorporates an adaptive algorithm to evaluate ophthalmic images for diagnostic screening to identify retinal diseases or conditions.

(b) *Classification*. Class II (special controls). The special controls for this device are:

(1) Software verification and validation documentation, based on a comprehensive hazard analysis, must fulfill the following:

(i) Software documentation must provide a full characterization of technical parameters of the software, including algorithm(s).

(ii) Software documentation must describe the expected impact of applicable image acquisition hardware characteristics on performance and associated minimum specifications.

(iii) Software documentation must include a cybersecurity vulnerability and management process to assure software functionality.

(iv) Software documentation must include mitigation measures to manage failure of any subsystem components with respect to incorrect patient reports and operator failures.

(2) Clinical performance data supporting the indications for use must be provided, including the following:

(i) Clinical performance testing must evaluate sensitivity, specificity, positive predictive value, and negative predictive value for each endpoint reported for the indicated disease or condition across the range of available device outcomes.

(ii) Clinical performance testing must evaluate performance under anticipated conditions of use.

(iii) Statistical methods must include the following:

(A) Where multiple samples from the same patient are used, statistical analysis must not assume statistical independence without adequate justification.

(B) Statistical analysis must provide confidence intervals for each performance metric.

(iv) Clinical data must evaluate the variability in output performance due to both the user and the image acquisition device used.

(3) A training program with instructions on how to acquire and process quality images must be provided.

(4) Human factors validation testing that evaluates the effect of the training program on user performance must be provided.

(5) A protocol must be developed that describes the level of change in device technical specifications that could significantly affect the safety or effectiveness of the device.

(6) Labeling must include:

(i) Instructions for use, including a description of how to obtain quality images and how device performance is affected by user interaction and user training;

(ii) The type of imaging data used, what the device outputs to the user, and whether the output is qualitative or quantitative;

(iii) Warnings regarding image acquisition factors that affect image quality;

(iv) Warnings regarding interpretation of the provided outcomes, including:

(A) A warning that the device is not to be used to screen for the presence of diseases or conditions beyond its indicated uses;

(B) A warning that the device provides a screening diagnosis only and that it is critical that the patient be advised to receive followup care; and

(C) A warning that the device does not treat the screened disease;

(v) A summary of the clinical performance of the device for each output, with confidence intervals; and

(vi) A summary of the clinical performance testing conducted with the device, including a description of the patient population and clinical environment under which it was evaluated.

Dated: January 14, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022-01147 Filed: 1/20/2022 8:45 am; Publication Date: 1/21/2022]